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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,713	04/04/2001	Matthew During	DUR01-NP001	3131

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EXAMINER
KATCHEVES, KONSTANTINA T

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/06/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/825,713	Applicant(s) DURING ET AL.	
	Examiner Konstantina Katcheves	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-23 are pending in the present application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 August 2002 has been entered.

Response to Amendment

Claims 1-19 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods drawn to mice and rats, does not reasonably provide enablement for methods drawn to the treatment of human subjects for the reasons of record set forth in the Office Action mailed 20 May 2002 and the reasons set forth below.

Response to Arguments

Claims 1-19 stand rejected under 35 U.S.C. 112, first paragraph, because the invention has not enabled one of skill in the art to make and use the invention for the entire scope claimed. As discussed in the Office Action mailed 20 May 2002 and the Office Action mailed 29 August 2001, the present invention while enabled for rats and mice is not enabled for all mammals, including humans.

As discussed in the previous Office Actions, the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. For Applicant's benefit, attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

The most relevant of these factors have been discussed in previous Office Actions. Therefore, the discussion below is limited to Applicant's response the present rejection.

Applicant's rebuttal relies almost exclusively on the proposition that the mouse and rat models are sufficient to support claims drawn to humans. Applicant has cited various references that disclose mouse and rat models and has referred to the specification wherein it discloses means of producing animal models. The fact that mouse and rat models are used in the art does not necessarily render the method claimed predictable such that one of skill in the art can make and use the invention without undue experimentation. The references cited by Applicant on page

11 of the response filed 23 August 2002 all relate to the use of either rat or mouse model. None of which disclose the use of their methods with human subjects. Moreover, none of these references disclose the grafting of stem cells or myeloid stem cells into a rat model. They either disclose treatment or rats with drugs or the grafting of fetal mesencephalic cells into rats. Therefore, these reference do not overcome the unpredictability in the art of stem cell replacement therapy.

Applicant also cites Björklund et al. (Nature Vol.3 no.6 2000) stating that: "the results of human patient trials are generally consistent with findings in experimental animals." Applicant should note that the results referred to in this passage relate to the treatment of animals and human subjects with grafted dopaminergic neurons. Unlike the present invention, which is drawn to the use of myeloid stem cells, these cells are differentiated dopaminergic neurons which are grafted directly to the site of the lesion. This statement does not consider the use of myeloid stem cells and the expression of a transgene that is contained within the stem cells of the claims. The nature of the present is complicated because, it involves undifferentiated cells which are used for the delivery of a transgene. Therefore, the present invention has two facets that are not considered in this statement by Björklund et al.: stem cell replacement therapy and gene therapy. Björklund et al. recognized that stem cell technology has to mature before human treatment is possible. Bjorklund et al. "agree that these [stem cells] may provide a new powerful tool for transplantation studies," however, they "believe that any clinical application of this new technology must await convincing preclinical data, no only to demonstrate efficacy by also to reveal the mechanism underlying any observed functional recovery."

Applicant traverses the press release from the National Institute of Neurological Disorders and Stroke on 09 January 2002, which recognizes the continuing need for research in the area of stem cell transplantation. Applicant asserts that the results of Björklund et al. (PNAS Vol.99 No.4 2002) show that 14 rats not only survived but were successfully treated following stem cell implantation. Applicant's assertions and teachings in the specification fail to satisfy several issues regarding the state of and predictability of the art. Applicant must show that the transgene contained in the stem cell is stable and expresses over a long period of time in the subject. In the case of stem cells or progenitor cells such as those of the present invention, the efficient gene transfer needs to be developed to ensure long-term production of the transgenic protein. Additionally, the transplanted cells must not trigger a host immune response, which would be detrimental to any gene transfer procedure. As previously discussed, Applicant has not disclosed how long these cells will express the gene of interest or how they will survive. A significant obstacle to the development of gene therapy is the targeted long-term expression of the transgene, which is what Applicant purports its genetically modified myeloid stem cells can do. See generally Martinez-Cerano et al. (TINS Vol.20 no.20 1997) and Verma et al. (Nature Vol. 389 1997). Gene therapy and stem cell therapy is unpredictable in nature such that it is difficult to extrapolate from animal models to human systems. Crystal (Science Vol. 270 1995) provides a long list of clinical trials that have yet to yield therapeutic benefits and further states that "humans are not simply large mice." See page 409. Moreover, the National Institute of Neurological Disorders and Stroke issued a press release after the mailing date of the prior office action. This press release discusses the results of a study by Ronald McKay, Ph.D. stating: "While the results suggest that ES cell-derived neurons may be useful for treating PD and other

neurological diseases, they are still preliminary, Dr. McKay says. Researchers need much more information about how the cells interact with the host brain and about their safety before similar strategies can be tested in humans." See http://www.ninds.nih.gov/news_and_events/pressrelease_stemcells_062002.htm?type=archived and Kim et al. (Nature Vol.418 2002) page 54 - page 55.

For the foregoing reasons, there is reason to believe that Applicant's results would not be predictive of results in human subjects. Therefore, one of skill in the art would be unable to make and use the invention commensurate with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Eglitis et al. (PNAS Vol.94 1997).

The invention of the instant claims is drawn to a method of the delivery of mammalian myeloid derived stem cells into the mammalian nervous system of a mammal. The invention further is drawn to the delivery of stem cells transfected with foreign genes. The method includes administering stem cells into a subject mammal, the migrating of the cells into the nervous system and the engrafting of the cells in the brain.

Eglitis et al. discloses the transplantation of myeloid cells marked with a retroviral vector into the brains of mice. These cells are capable of migration to discrete parts of the brain and express the exogenous gene. Eglitis further discloses that myeloid derived cells acquire microglial antigenic markers and finds hematopoietically derived microglia in the brains of rats. See pages 4080 - 4081 and page 4082, column 1.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (703) 305-1999. The examiner can normally be reached on Monday through Friday 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3388.

Konstantina Katcheves
October 30, 2002

JAMES KETTER
PRIMARY EXAMINER